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(54) **A method for preparing resinates**

(57) A highly productive and environmentally friendly method of loading pharmaceutically active substances onto ion exchange resins using water and, if desired, a water miscible or water-immiscible solvent.

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Description

BACKGROUND OF THE INVENTION

[0001] The present invention relates to a method for the aqueous loading of poorly water soluble and soluble pharmaceutically active substances onto ion exchange resins.

[0002] It is well know in the art that using a complex formed between a polymeric material and an active substance can be beneficial. Such benefits can include changes in the release rate of drugs, taste masking of bitter drugs, control of the site of administration of drugs, control of the release of flavor substances, and stabilization of unstable substances.

[0003] The preparation of an active substance/ion exchange resin complex is called loading. The ion exchange resins complexed with the active substance are called resinates. The methods for loading have been varied, but in many cases are either problematic or limited in their application.

[0004] The typical method for loading active substances onto an ion exchange resin is to dissolve an acidic or basic, ionizable active substance in water, and then mix it with a suitable ion exchange resin. See, US2,990,332. The active substance is absorbed into the resin by the mechanism of ion exchange. The extent of loading will depend on several factors, including the rate of diffusion, the equilibrium constant, temperature, and the presence of other ions. The water is then removed by filtration, and the ion exchange resin dried by heating. As a general rule, anion exchange resins are useful for the loading of acidic substances, and cation exchange resins are useful for loading basic substances.

[0005] The need to dissolve the active substance to be loaded can lead to very large volumes of solution if the active substance has poor solubility in the loading medium. This leads to very low productivity in a commercial scale process. To overcome this problem, water miscible organic co-solvents such as ethanol are frequently used to increase the solubility and to reduce the total volume of solution. Introduction of these co-solvents into the process can add significant cost, because they are typically not recovered. They can increase the amount of hazardous waste generated, and introduce processing problems related to flammability and toxicity.

[0006] In the currently used commercial processes for making the resinates of active substances, said active substance is loaded onto a powdered, anion or cation ion exchange resin. The loading is performed in a predominantly aqueous system, whereby the active substance becomes immobilized on the resin by reaction with the functional groups of the resin. Use of an aqueous system for the loading has the disadvantage that the resulting slurry has to be dewatered and dried. This is currently achieved in a number of different ways, e. g., dewater in a decanter, and then dry in a vacuum dryer; or evaporate the water directly from the slurry in a vacuum distillation apparatus; and evaporate the water directly from the slurry using a spray dryer. There are problems associated with each of these methods. The decanter operation is made difficult because the ion exchange resin contains a significant fraction of very fine particles (<40 micron), and wet-cakes from such decanters can still contain >60% water by weight. The spray dryer and vacuum distillation operations are energy wasteful because all the water is removed by conversion to water vapor. Also, these methods can lead to particle agglomeration. Avoidance of these problems by using typical organic solvents leads to problems of toxicity from the residual solvent, safety problems from flammability, and environmental problems from vapor emissions and waste disposal.

[0007] The use of non-aqueous solvents as media for ion exchange reactions has been reported. See *"Ion Exchange Resins"* by Robert Kunin, p. 310, published by Robert E. Krieger Publishing Co, 1990. However, reaction times are reported to be very long for non-swelling solvents. Further, the solvents typically used are not optimum for industrial scale because they are flammable, or toxic, or difficult to remove efficiently, or difficult to reuse, or environmentally unacceptable, or high cost.

[0008] Many drug substances are hydrophobic and are poorly soluble in water. While this can be somewhat advantageous for absorption from solution into the gastrointestinal system, the actual dissolution of such drugs into physiological fluids can be very inefficient. This can result not only from a low solubility, but also a low rate of dissolution. This low rate of dissolution is itself the result of poor wettability of the hydrophobic solid, and the thermodynamic barrier caused by high crystal lattice energy which is difficult to overcome with water. This poor dissolution into physiological fluids can result in very poor and/or variable bioavailability of the drugs. Methods to improve the dissolution can thereby improve bioavailability.

[0009] A number of solutions have been explored, including grinding the drug to very small particle size (WO99/30687) and supplying it as a solution in oils (EP0306236B1). Each of these techniques has disadvantages. For example, not all drugs can be ground to very fine particle size due to low melting point or heat sensitivity. Dissolution in oils or dispersion in other matrices severely restricts the formulation options. There is a need for a method to improve dissolution that does not suffer these disadvantages.

[0010] The use of ion exchange resins to improve the rate of dissolution of weakly ionic compounds was reported by Irwin. *See,* Irwin, et al, Drug Deliv. and Ind. Pharm, 16(6), 883 (1990). Irwin observed faster dissolution of mefenamic acid from a powdered, strong base anion exchange resin when compared to a solid suspension. The loading method used by Irwin employed an aqueous medium as known to those skilled in the art.

[0011] Thus, there is a need in the art for an active ingredient loading method that is environmentally

friendly, safe, low cost, and capable of high productivity. There is also need for a method that improves the dissolution of poorly soluble drugs that is not limited by melting point or temperature sensitivity, and is compatible with most existing formulation methods. Applicants have surprisingly discovered how to load poorly soluble or soluble active substances onto ion exchange resins using water, water miscible, and water immiscible solvents or mixtures thereof. Further, when said miscible and immiscible solvents are omitted, and only water is used, the amount of water needed is surprisingly very much less than that required to completely dissolve the active substance. Finally, Applicants have also unexpectedly discovered that the resinates of poorly soluble drugs made by the process of the present invention have a faster drug dissolution rate under physiological conditions.

[0012] The following terms have the following meanings herein:

[0013] The term "solubility," as used herein, means solubility as defined in the US Pharmacopoeia, 24, pg. 10. For the purposes of this invention the descriptor 'poorly soluble' will be used to describe substances that are very slightly soluble or practically insoluble in water by the USP definition. This solubility is <1 part of solute per 1000 parts of solvent. The descriptor 'soluble' will be used to describe substances with a solubility >1 part solute per 1000 parts solvent.

[0014] The term "water retention capacity" as used herein is used to describe the maximum amount of water that an ion exchange resin can retain within the polymer phase and in any pores. (ASTM D2187: Standard Test Methods for Physical and Chemical Properties of Particulate Ion Exchange Resin. Test Method B: Water Retention Capacity)

[0015] The term "resinate," as used herein, means an active substance/ion exchange resin complex.

[0016] The terms "loaded" and "loading" as used here-in mean the preparation of a resinate. The amount of loading means the amount of active substance incorporated into the resin to form a resinate.

[0017] Further, ion exchange resins are characterized by their capacity to exchange ions. This is expressed as the "Ion Exchange Capacity." For cation exchange resins the term used is "Cation Exchange Capacity," and for anion exchange resins the term used is "Anion Exchange Capacity." The ion exchange capacity is measured as the number equivalents of an ion that can be exchanged and can be expressed with reference to the mass of the polymer (herein abbreviated to "Weight Capacity") or its volume (often abbreviated to "Volume Capacity"). A frequently used unit for weight capacity is "milliequivalents of exchange capacity per gram of dry polymer." This is commonly abbreviated to "meq/g."

[0018] Ion exchange resins are manufactured in different forms. These forms can include spherical and non-spherical particles with size in the range of 0.001mm to 2mm. The non-spherical particles are frequently manufactured by grinding of the spherical particles. Products made in this way typically have particle size in the range 0.001mm to 0.2mm. The spherical particles are frequently known in the art as 'Whole Bead.' The non-spherical particles are frequently known in the art as 'Powders.'

STATEMENT OF THE INVENTION

[0019] The present invention relates to a method for preparing a resinate comprising the steps of:

a. blending a poorly water soluble or soluble active substance with an ion exchange resin and a solvent selected from the group consisting of water, a water miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;
b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.

DETAILED DESCRIPTION OF THE INVENTION

[0020] The present invention relates to a method for preparing a resinate comprising the steps of:

a. blending a poorly water soluble or soluble active substance with an ion exchange resin and a solvent selected from the group consisting of water, a water miscible solvent, a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;
b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.

[0021] Ion exchange resins useful in the practice of the present invention include, but are not limited to, anionic exchange resins and cationic exchange resins. Preferably, said resins are suitable for human and animal ingestion.

[0022] Preferred anionic exchange resins include, but are not limited to, styrenic strongly basic anion exchange resins with a quaternary amine functionality having a weight capacity of 0.1 to 15 meq/g, and styrenic weakly basic anion exchange resins with a primary, secondary, or tertiary amine functionality having a weight capacity of 0.1 to 8.5 meq/g, and acrylic or methacrylic strongly basic anion exchange resins with a quaternary amine functionality having a weight capacity of 0.1 to 12 meq/g, and acrylic or methacrylic weakly basic anion exchange resins with a primary, secondary, or tertiary amine functionality having a weight capacity of 0.1 to 12 meq/g, and allylic and vinylic weakly basic anion exchange resins with a primary, secondary, or tertiary amine functionality having a weight capacity of 0.1 to 24 meq/g, that are suitable for human and animal ingestion.

[0023] Most preferred anionic exchange resins include, but are not limited to, styrenic anion exchange resins with quaternary amine functionality with weight capacity of 0.1 to 6 meq/g and acrylic anion exchange resins with tertiary amine functionality with weight capacity of 0.1 to 12 meq/g, that are suitable for human and animal ingestion.

[0024] Preferred cationic exchange resins include, but are not limited to, styrenic strongly acidic cation exchange resins with sulfonic or phosphonic acid functionalities having a weight capacity of 0.1 to 8 meq/g; and styrenic weakly acidic cation exchange resins with carboxylic or phenolic acid functionalities having a weight capacity of 0.1 to 8.5 meq/g; and acrylic or methacrylic weakly acidic cation exchange resins with a carboxylic or phenolic acid functionality with a weight capacity of 0.1 to 14 meq/g, that are suitable for human and animal ingestion.

[0025] Most preferred cationic exchange resins include, but are not limited to, styrenic weakly acidic cation exchange resin with a phenolic functionality with a weight capacity of 0.1 to 8.5 meq/g; and a styrenic strongly acidic cation exchange resin with a sulfonic acid functionality with weight capacity of 0.1 to 8 meq/g, or a methacrylic weakly acidic cation exchange resin with a carboxylic acid functionality with weight capacity of 0.1 to 12 meq/g.

[0026] Ion exchange resins useful in this invention have a moisture content between 0% and the water retention capacity of said resin.

[0027] Ion exchange resins useful in this invention are in powder or whole bead form.

[0028] Strongly acidic and weakly acidic cation exchange resins useful in the practice of the present invention are in the acid form or salt form or partial salt form.

[0029] Strongly basic anion exchange resins useful in this invention are in the salt form.

[0030] Weakly basic anion exchange resins useful in this invention are in the free-base form or salt form.

[0031] Water soluble or poorly soluble active substances useful in the practice of the present invention include, but are not limited to, pharmaceutically active substances, vitamins, flavors and fragrances, that have acidic or basic ionizable groups.

[0032] Pharmaceutically active substances include, but are not limited to, indomethacin, salicylic acid, ibuprofen, sulindac, piroxicam, naproxen, timolol, pilocarpine, acetylcholine, dibucaine, thorazine, promazine, chlorpromazine, acepromazine, aminopromazine, perazine, prochlorperazine, trifluoroperazine, thioproperazine, reserpine, deserpine, chlorprothixene, tiotixene, haloperidol, moperone, trifluorperidol, timiperone, droperidol, pimozide, sulpiride, tiapride, hydroxyzine, chlordiazepoxide, diazepam, propanolol, metoprolol, pindolol, imipramine, amitryptyline, mianserine, phenelzine, iproniazid, amphetamines, dexamphetamines, fenproporex, phentermine, amfepramone, pemoline, clofenciclan, cyprodenate, aminorex, mazindol, progabide, codergoctine, dihydroergocristine, vincamone, citicoline, physostigmine, pyritinol, meclofenoxate, lansoprazole, nifedipine, risperidone, clarithromycin, cisapride, nelfinavir, midazolam, lorazepam, nicotine, ciprofloxacin, quinapril, isotretinoin, valcyclovir, acyclovir, delavirdin, famciclovir, lamivudine, zalcitabine, osteltamivir, abacavir, prilosec, omeprazole, prozac, zantac, lisinopril.

[0033] The preferred water insoluble or poorly soluble pharmaceutically active substances include, but are not limited to indomethacin, lansoprazole, nifedipine, risperidone, clarithromycin, cisapride, nelfinavir, midazolam, lorazepam, ciprofloxacin, quinapril, and isotretinoin.

[0034] The most preferred water insoluble or poorly soluble pharmaceutically active substances are indomethacin, nelfinavir, and midazolam.

[0035] Vitamins useful in the practice of the present invention include, but are not limited to, A, C, E, and K.

[0036] Flavors and fragrances useful in the practice of the present invention include, but are not limited to, vanillin, methyl salicylate, thymol, ethyl vanillin.

[0037] The preferred solvents useful in the practice of the present invention are selected from the group consisting of water, water miscible solvents, water immiscible solvents and mixtures thereof.

[0038] Water miscible solvents useful in the practice of the present invention include, but are not limited to, methanol, ethanol, isopropanol, n-propanol, acetone, dimethylformamide, tetrahydrofuran, dimethyl sulfoxide, dimethyl ether, and acetic acid.

[0039] The preferred water miscible solvents are ethanol, isopropanol, n-propanol, and dimethyl ether.

[0040] The most preferred water miscible solvent is ethanol.

[0041] Water immiscible solvents useful in the practice of the present invention include, but are not limited to hydrocarbons, halogenated hydrocarbons, ethers, ketones, and esters having boiling points, at atmospheric pressure between 100°C and -100°C.

[0042] The preferred water immiscible solvents are fluorinated hydrocarbon solvents having boiling points, at atmospheric pressure between 30°C and -100°C

[0043] The more preferred water immiscible solvents are:

trifluoromethane (CF_3H);
fluoromethane (CH_3F);
difluoromethane (CF_2H_2);
1,1-difluoroethane (CF_2HCH_3);
1,1,1-trifluoroethane (CF_3CH_3);
1,1,1,2-tetrafluroethane (CF_3CFH_2)
pentafluoroethane (CF_3CF_2H);
1,1,1,2,2-pentafluorpropane ($CF_3CF_2CH_3$);
1,1,1,2,3-pentafluorpropane ($CF_3CFHCFH_2$);
1,1,1,2,2,3-hexafluoropropane ($CF_3CF_2CFH_2$);
1,1,1,2,3,3-hexafluoropropane (CF_3CFHCF_2H);

1,1,1,3,3,3-hexafluropropane ($CF_3CH_2CF_3$);
1,1,2,2,3,3-hexafluoropropane ($CF_2HCF_2CF_2H$);
1,1,1,2,2,3,3-heptafluoropropane ($CF_3CF_2CF_2$);
1,1,1,2,3,3,3-heptafluoropropane (CF_3CFHCF_3);

[0044] The most preferred water immiscible solvent is 1,1,1,2-tetrafluoroethane (CF_3CFH_2), also known as TFE. This solvent has a boiling point of -26.5°C at atmospheric pressure, is of low toxicity, is non-flammable, and is non ozone depleting.

[0045] The preferred range of ratios of ion exchange resin to solvent is 1:1 to 1:1000, the more preferred range is 1:1.5 to 1:100, and the most preferred range is 1:2 to 1:5.

[0046] Preferably, the loading of active substance in the resinate of the present invention is 5-100% of the ion exchange capacity of the resin, more preferably it is 10-90% of the ion exchange capacity of the resin, and most preferably it is 15-80% of the ion exchange capacity of the resin.

[0047] The preferred pressure range for the practice of the present invention is 5 to 35,000 kPascals, the more preferred range is 100 to 5000 kPascals, and the most preferred range is 350 to 700 kPascals.

[0048] The preferred temperature range for the practice of the present invention is 10°C to 100°C, the more preferred range is 0°C to 80°C, and the most preferred range is 5°C to 30°C.

[0049] Preferably, the time to prepare a resinate of the present invention is from 1 second to 48 hours, more preferably from 5 minutes to 4 hours, and most preferably from 5 minutes to 30 minutes.

[0050] While Example 1 surprisingly illustrates that a poorly soluble drug can be loaded onto an ion exchange resin with less water than is required to completely dissolve said drug, the loading process takes about 2 hours and the mixture must be dewatered.

[0051] However, the addition of a water-immiscible or water miscible solvent as described hereinabove reduces the loading time to between 1 minute and 20 minutes, and eliminates the need to dewater the mixture. For example, in a preferred embodiment of the invention, the amount of water required is such that it does not exceed the water retention capacity of the ion exchange resin. In this way there is no separate water phase in the mixture. Because of the property of ion exchange resins to absorb water up to the water retention capacity the water can either be present in the ion exchange resin at the start of the process, or added as a separate ingredient to the mixture. The water immiscible solvent can be removed from the final mixture either by filtration, or by vaporization. The vaporization can be achieved by using heat, or by reducing the pressure, and providing a heat source to maintain the temperature of the solution between room temperature and the atmospheric pressure boiling point of said solvent. Specifically, the active substance, a suitable hydrated anion or cation exchange resin, and TFE are mixed at a pressure of about 520 kPascals to maintain said TFE in the liquid state. The mixture is stirred at room temperature for between 5 and 20 minutes. During this period the active substance rapidly loads onto the ion exchange resin, such that there is no solid active substance left in the mixture, and the amount of active substance dissolved in the TFE is insignificantly small. The TFE is then removed by reducing the pressure such that the TFE boils. The TFE vapor can be recovered either by using a condenser at less than the boiling point of the TFE, or by using a compressor and condenser. Both recovery methods are well known in the art. The TFE can then be re-used.

[0052] The ion exchange resin loaded with poorly soluble active substance prepared using TFE has very unexpectedly been found to exhibit an improved dissolution rate of said active substance over those made using the prior art as described in Irwin *et al*, Drug Deliv and Ind Pharm, 16(6), 883 (1990). The rate of dissolution of the active substance, prepared according to the present invention, under physiological conditions is greatly increased when compared to similar compositions made using the prior art. This is illustrated by Examples 7-10. In these examples, the poorly soluble drug indomethacin is loaded on a weakly basic anion exchange resin either by the method of this invention using TFE, or by using an aqueous ethanol solution to represent the prior art. The samples were tested, both with and without drying, in a dissolution test apparatus using simulated intestinal fluid. The data demonstrated that the resinates made by the method of the present invention released the indomethacin at a rate approximately double that of the materials made using the prior art.

[0053] The following non limiting examples illustrate the practice of the present invention.

EXAMPLE 1 - Water-only loading:

[0054] Add 0.5 g of indomethacin, a poorly soluble active substance, and 1.5g of an acrylic anion exchange resin with tertiary amine functionality and a weight capacity between 5.8 and 6.2 meq/g, such as Amberlite IRA67, available from the Rohm and Haas Company, in its fully hydrated state to a 25 ml vial. Add 6 g of water to the mixture, close the vial and shake the mixture. After 2 hours the indomethacin will have disappeared and the ion exchange resin will be yellow. Drain the water from the mixture, to yield the wet resinate.

[0055] This experiment illustrates the very large reduction in required reaction volume achieved by the invention over the prior art. The solubility of indomethacin in water is 14ppm so that approximately 37kg of water would be required to completely dissolve the amount of indomethacin used in this example. For a commercial scale operation this decrease in required volume would represent a 6000 fold increase in productivity over the prior art.

EXAMPLE 2 - TFE with dried resin

[0056] Into a vessel that can be evacuated and can operate at least 750 kPascals and is equipped with a stirrer, charge 1.3g of a finely ground acrylic anion exchange resin with tertiary amine functionality and a weight capacity between 5.8 and 6.2 meq/g that has been dried to <5% moisture, such as derived from the resin Amberlite IRA67, available from the Rohm and Haas Company. To the same vessel charge 1g of indomethacin. Evacuate the air from the vessel, and then introduce 50g of 1,1,1,2-tetrafluoroethane (TFE) so that at the end of the addition the pressure is approximately 520 kPascals and the temperature is 20°C, such that the TFE is in the liquid state. Stir the mixture for 120 minutes maintaining the temperature and pressure. At the end of this period, stop the stirrer and allow the mixture to stand for a few minutes. It will be noted that the resin, which is still white, will float to the surface of the TFE, and the undissolved indomethacin solid will sink to the bottom. These observations indicated that no significant loading has taken place.

EXAMPLE 3 - TFE wet loading

[0057] Proceed as in Example 2, except add 1.7g of water to the mixture. This is sufficient water to hydrate the ion exchange resin, but not sufficient to form a separate liquid water layer. After stirring for 10minutes stop the stirrer and allow the mixture to stand for a few minutes. It will be noted that the resin, now yellow in color, will float to the surface, and that there will be no indomethacin on the bottom of the vessel. Carefully remove approximately one half of the TFE as a liquid sample, without including any of the resinate. Remove the TFE from this sample by evaporation. It will be noted that there is no significant solid residue left after the TFE has been removed. These observations indicate that all the indomethacin loaded onto the resin.

EXAMPLE 4 - Dichlorethane loading

[0058] Proceed as in Example 1, except use 7g of dichloroethane. After shaking for 10 minutes, it will be noted that the resin is now yellow, and that there is no solid indomethacin present. This observation indicates the indomethacin loaded onto the ion exchange resin.

EXAMPLE 5 - Pentane loading

[0059] Proceed as in Example 1, except use 3.5g of pentane instead of dichloroethane. After shaking for 20 minutes, it will be noted that the resin is now yellow, and that there is no solid indomethacin present. This observation indicates the indomethacin loaded onto the ion exchange resin

EXAMPLE 6 - Preparing a resinate of nelfinivir and Amberlite IRP64

[0060] The same as Example 3, except use 1g of Nelfinivir, 1.4g of water, and 1.6g of a dried, ground methacrylic weakly acidic cation exchange resin with carboxylic acid functionality with weight capacity between 10.1 and 11.1 meq/g (such as Amberlite IRP64, available from the Rohm and Haas Company).

[0061] Dissolution testing samples were prepared accordingly:

EXAMPLE 7 - Preparation of the sample of the present invention for dissolution testing.

[0062] In the same equipment as used in Example 2, charge 3g of an acrylic anion exchange resin with tertiary amine functionality and a weight capacity between 5.8 and 6.2 meq/g, such as Amberlite IRA67, available from the Rohm and Haas Company, in its fully hydrated state, whole bead form. To the same vessel charge 1g of indomethacin. Evacuate the air from the vessel, and then introduce 50g of 1,1,1,2-tetrafluoroethane (TFE) so that at the end of the addition the pressure is approximately 520 kPascals and the temperature is 20°C, such that the TFE is in the liquid state. Stir the mixture at room temperature for 10 minutes. During this period the resin will change to a yellow color, indicating indomethacin loading. Reduce the pressure in the loading vessel by venting it to the atmosphere to remove the TFE. There remains a water-wet resinate, that is indomethacin loaded onto the anion exchange resin.

EXAMPLE 8 - Preparation of the sample of the present invention for dissolution testing.

[0063] Proceed as in Example 7, except dry the resinate in a vacuum oven at 60°C for 4 hours.

EXAMPLE 9 - Preparation of a sample of the prior art for dissolution testing.

[0064] Prepare a solution of 1g of indomethacin in 200ml of 50% aqueous ethanol. To this add 3g of an acrylic anion exchange resin with tertiary amine functionality and a weight capacity between 5.8 and 6.2 meq/g (such as Amberlite IRA67, available from Rohm and Haas Company, Philadelphia, Pennsylvania) in its fully hydrated state, whole bead form. Shake the mixture overnight at room temperature. During this period the yellow solution will lose most of its color, and the resin will become yellow. Drain the solution from the mixture, and analyze it for indomethacin using a uv/vis spectrometer at a wavelength of 318nm, such as described in US Pharmacopoeia, USP24 p. 874. The analysis will indicate approximately 0.1g of the indomethacin was left in solution, and did not load onto the resin.

EXAMPLE 10 - Preparation of a sample of the prior art for dissolution testing.

[0065] Proceed as in Example 9, except dry the resinate in a vacuum oven at 60°C for 4 hours.

[0066] Dissolution testing performed on Examples 7-10.

[0067] For samples of each of the Examples 7-10, weigh out sufficient resinate to give 25mg of indomethacin. Add the resinate to 750ml of Simulated Intestinal Fluid TS, as defined by USP24, except that no purified pancreatin is included, at room temperature. Stir the mixture at 250rpm and take samples at 0, 10, 20, 45, and 120 minutes. Analyze the samples for indomethacin using uv/vis spectrometry. The data obtained is illustrated in TABLE 1 below:

TABLE 1-

% Release of Indomethacin					
Time, (mins)	**0**	**10**	**20**	**45**	**120**
Example 7	0	12.1	14.7	23.2	35.0
Example 8	0	14.6	18.3	28.5	41.6
Example 9	0	8.8	8.8	14.3	25.5
Example 10	0	7.3	7.3	12.1	22.0

[0068] While not intending to be bound by theory, microscopic examination of the resinate from Examples 7 and 8, as compared with Examples 9 and 10, reveals that the increase in the rate of dissolution of the active ingredient is caused by an anisotropic distribution of the active ingredient in the resinate particles. This distribution is such that there is a higher concentration of active ingredient on and near the surface of the particle than there is deeper within the particle. This reduces the average distance (diffusion path) that a molecule has to diffuse before it reaches the surface, at which point it dissolves into the bulk liquid phase. This reduction in the diffusion path results in faster overall release of the active ingredient. The anisotropic distribution is a direct result of the loading method, which produces a very high localized concentration of active substance at the particle surface, such that diffusion into the particle is not fast enough to give isotropic distribution.

Example 11 - Use of a water miscible solvent

[0069] The same as Example 1 except that the instead of adding water, add 2.5g of water and 2.5g of ethanol. The indomethacin will load within 2 hours. The supernatant at the end of the experiment will contain approximately 0.003g of indomethacin that did not load.

Claims

1. A method for preparing a resinate comprising the steps of:

   a. blending a poorly water soluble or soluble active substance with an ion exchange resin and a solvent selected from the group consisting of water, a water miscible solvent, and a water-immiscible solvent or mixtures thereof to form an active substance/resin/solvent mixture;
   b. maintaining said mixture, at a pressure and temperature that maintains said mixture in the liquid state, for 1 second to 48 hours.

2. A method according to Claim 1 wherein the ratio of resin to solvent is 1:1 to 1:1000.

3. A method according to Claim 2, wherein the ratio of resin to solvent is 1:1.5 to 1:100.

4. A method according to Claim 3, wherein the ratio of resin to solvent is 1:2 to 1:5.

5. A method according to Claim 3, wherein the active substance is loaded at 5-100% of the ion exchange capacity of the resin.

6. A method according to Claim 3, wherein the active substance is loaded at 10-90% of the ion exchange capacity of the resin.

7. A method according to Claim 3, wherein the active substance is loaded at 15-80% of the ion exchange capacity of the resin.

8. A method according to Claim 1 wherein the water immiscible solvent is a hydrocarbon, halogenated hydrocarbon, ether, ketone, or ester, mixture thereof, having a boiling point, at atmospheric pressure between 100°C and -100°C.

9. A method according to Claim 8 wherein the water immiscible solvent is a fluorinated hydrocarbon having a boiling point, at atmospheric pressure between 30°C and -100°C.

10. A method according to Claim 9 wherein the water immiscible solvent is 1,1,1,2-tetrafluoroethane.

11. A method according to Claim 1 wherein the ion exchange resin is an anionic exchange resin or cationic exchange resin.

12. A method according to Claim 11, wherein the ion exchange resin is a cationic exchange resin.

13. A method according to Claim 11, wherein the ion

exchange resin is an anionic exchange resin.

14. A method according to Claim 1 wherein the water miscible solvent is a selected from the group consisting of ethanol, isopropanol, n-propanol and dimethyl ether.

15. A method for administering a poorly soluble medicament comprising administering an effective amount of a resinate prepared according to Claim 1.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 01 30 6421

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 5 032 393 A (DOUGLAS STEPHEN J ET AL) 16 July 1991 (1991-07-16) * column 4, line 35 - line 45 *	1-3,5-7, 11,12,15	A61K47/48 A61K31/405
X	EP 0 431 759 A (GLAXO GROUP LTD) 12 June 1991 (1991-06-12) * claims * * examples 1-3 *	1-7,11, 12,14,15	
X	EP 0 911 039 A (MEDEVA PHARMACEUTICAL MANUFACT) 28 April 1999 (1999-04-28) * example 1 *	1-7,11, 12,15	
X	GB 1 101 366 A (HOFFMANN LA ROCHE) 31 January 1968 (1968-01-31) * page 2, left-hand column, line 34 - right-hand column, line 126 *	1-8,11, 12,15	

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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

–

Reason for the limitation of the search:

Although claim 15 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
MUNICH	5 November 2001	Zimmer, B

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 01 30 6421

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	GARCIA-ENCINA G ET AL: "IN VIVO EVALUATION OF NYLON-COATED DICLOFENAC-RESIN COMPLEXES" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 23, no. 3, 1 March 1993 (1993-03-01), pages 201-207, XP000343200 ISSN: 0168-3659 * page 202, right-hand column, paragraph 2 *	1,11, 13-15	
X	WO 00 40224 A (CLANCY MAURICE JOSEPH ANTHONY ;ELAN CORP PLC (IE); CODD JANET ELIZ) 13 July 2000 (2000-07-13) * example 3 *	1,2,5-7, 11,13,15	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 6421

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

05-11-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5032393 A	16-07-1991	AT 401614 B	25-10-1996
		AT 112089 A	15-03-1996
		AU 624613 B2	18-06-1992
		AU 3461789 A	16-11-1989
		BE 1002159 A5	14-08-1990
		CA 1337272 A1	10-10-1995
		CH 679011 A5	13-12-1991
		CN 1037651 A ,B	06-12-1989
		CY 1781 A	20-10-1995
		DE 3915347 A1	16-11-1989
		DK 229489 A	12-11-1989
		ES 2011573 A6	16-01-1990
		FI 892248 A ,B,	12-11-1989
		FR 2631232 A1	17-11-1989
		GB 2218333 A ,B	15-11-1989
		GR 89100314 A ,B	12-03-1990
		HK 45094 A	13-05-1994
		HR 940626 A1	28-02-1997
		HU 50036 A2	28-12-1989
		HU 204994 B	30-03-1992
		HU 9500512 A3	30-10-1995
		IE 60722 B	10-08-1994
		IL 90245 A	12-04-1994
		IT 1232831 B	05-03-1992
		JP 2111719 A	24-04-1990
		JP 2944678 B2	06-09-1999
		LU 87515 A1	12-06-1990
		MX 15983 A ,B	01-10-1993
		NL 8901188 A	01-12-1989
		NO 175131 B	30-05-1994
		NZ 229064 A	23-12-1991
		PH 27612 A	31-08-1993
		PL 279377 A1	22-01-1990
		PT 90523 A ,B	30-11-1989
		SE 508343 C2	28-09-1998
		SE 8901671 A	12-11-1989
		SG 48194 G	25-11-1994
		RU 2033155 C1	20-04-1995
		US 5219563 A	15-06-1993
		YU 97189 A1	30-06-1990
		ZA 8903463 A	28-03-1990
EP 0431759 A	12-06-1991	AT 99925 T	15-01-1994
		AU 6652790 A	16-05-1991
		CA 2029667 A1	11-05-1991
		DE 69005993 D1	24-02-1994

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 6421

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

05-11-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0431759 A		DE 69005993 T2	05-05-1994
		DK 431759 T3	28-02-1994
		EP 0431759 A1	12-06-1991
		ES 2047864 T3	01-03-1994
		JP 3206037 A	09-09-1991
EP 0911039 A	28-04-1999	US 5980882 A	09-11-1999
		CA 2234282 A1	16-10-1998
		EP 0911039 A2	28-04-1999
GB 1101366 A	31-01-1968	BE 685589 A	17-02-1967
		DE 1617513 A1	23-12-1970
		DK 111277 B	15-07-1968
		FI 45726 B	31-05-1972
		FR 6063 M	27-05-1968
		FR 1493798 A	08-12-1967
		IL 26306 A	19-02-1970
		IT 1053660 B	10-10-1981
		JP 50007079 B	20-03-1975
		MY 5969 A	31-12-1969
		NL 6610569 A	21-02-1967
		NO 120752 B	30-11-1970
		SE 351978 B	18-12-1972
WO 0040224 A	13-07-2000	AU 1998200 A	24-07-2000
		EP 1140037 A1	10-10-2001
		WO 0040224 A1	13-07-2000

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82